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Elastic Fiber Degeneration in Costello Syndrome

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Clinical and pathological observations of a 6-month-old-boy with Costello syndrome are reported. The main clinical findings were loose skin of the neck, hands, and feet, deep palmar and plantar creases, typical "coarse" face with thick lips and macroglossia, relative macrocephaly, mental retardation, short stature, arrhythmia, large size for gestational age, and poor feeding. At age 6 months he died of rhabdomyolysis. The major pathological findings were fine, disrupted, and loosely-constructed elastic fibers in the skin, tongue, pharynx, larynx, and upper esophagus, but not in the bronchi, alveoli, aorta, or coronary arteries. Hyperplasia of collagen fibers in the skin, hyperplasia of the mucous glands in the bronchus, narrowing of the pulmonary artery, degeneration of the atrial conduction system, calcification and ballooning of skeletal muscle fibers with infiltration of macrophages, and myoglobin depositions in the collecting ducts in the kidney were also observed. The degeneration of elastic fibers was confirmed in the skin of a second Costello syndrome patient. Expression of elastin mRNA in the patient's fibroblasts was normal in size and amount. Given that elastic fiber degeneration was observed in the tissues with clinical symptoms, we speculate that a defect of elastic fibers, possibly relating to alternative splicing in the elastin gene or to defects in elastin microfibrils, might be involved in the pathogenesis of Costello syndrome.

KEY WORDS: Costello syndrome, elastic fiber disruption, elastin, arrhythmia, rhabdomyolysis

INTRODUCTION

Costello syndrome is a rare congenital disorder characterized by loose skin of the neck, hands, and feet, "coarse" face, curly hair, mental retardation, short stature, relative macrocephaly, cardiomyopathy, dysrhythmia, and nasal papillomata. Since Costello first described these clinical features as a new syndrome in 1971 and 1977 [Costello, 1977], over 20 cases have been reported in the literature [Costello, 1977; Hall et al., 1990; Der-Kaloustian et al., 1991; Martin and Jones, 1991; Berberich et al., 1991; Borochowitz et al., 1992; Di-Rocco et al., 1993; Izumikawa et al., 1993; Kondou et al., 1993; Patton and Baraitser, 1993; Philip and Mancini, 1993; Say et al., 1993; Teebi and Shaabani, 1993; Yoshida et al., 1993; Zampino et al., 1993; Johnson et al., 1993; Okamoto et al., 1994; Davies and Hughes, 1994]. These reports have established this syndrome as a clinical entity; however, nothing is known about the underlying pathogenesis of this disease.

In the related syndromes of cutis laxa, loose skin is the main finding [Pope, 1993]. Within a diagnostic category of cutis laxa, patients with heterogeneous disorders are included, and Costello syndrome is differentiated clinically by a distribution of loose skin mainly in the hands, feet, and neck but not in the body, typical facial appearance, growth disturbance, and cardiac involvement. Most patients with cutis laxa show disruption of elastic fibers pathologically, and in fibroblasts the mRNA that codes for the tropoelastin, a component of elastic fibers, was reported to be decreased [Olsen et al., 1988; Sephel et al., 1989; Hatamochi et al., 1991]. In addition to cutis laxa, abnormalities of the elastin gene have been detected in Williams syndrome [Ewart et al., 1993]. With regard to Costello syndrome, there have been several descriptions of skin histology in affected patients; two have indicated that elastic fibers were intact [Patton and Baraitser, 1993; Davies and Hughes, 1994], while the others made no mention of them [Costello, 1977; Der-Kaloustian, 1991; Di-Rocco et al., 1993; Martin and Jones, 1991; Philip and Mancini, 1993; Say et al., 1993; Yoshida et al., 1993].

Here we report the clinical manifestations in a 6-month-old-boy with Costello syndrome, and the results of pathological examinations of his autopsied tissues.

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The major pathological finding was degradation of the elastic fibers in some but not all examined tissues. The expression of elastin mRNA was also evaluated, and a potential etiology of this syndrome involving elastin defects is discussed.

CLINICAL REPORT

Patient 1

This was the only son of a nonconsanguineous 23-year-old mother and 32-year-old father. He was born at 38 weeks of gestation after a pregnancy complicated by polyhydramnios and fetal distress. His birthweight was 4,148 g, and an Apgar score was 7 at 5 min. He was intubated for 3 days because of massive aspiration syndrome. Premature ventricular beats were frequently observed for the first several days; afterwards, frequent premature atrial contractions also occurred. The baby was fed parenterally because the suck was poor and there was respiratory stridor.

At age 6 months, body growth was poor; weight was 5,730 g (−2.7 SD), height was 61.0 cm (−2.9 SD), and head circumference (OFC) was 40.5 cm (−2.1 SD). The infant's development was delayed, and he could not control his head. He had various clinical findings such as "coarse" face (Fig. 1a) with prominent forehead, hypertelorism, epicanthal folds, depressed nasal bridge, large ears, high-arched palate, soft tissue swelling of the oral cavity, bifid uvula, skin indentation of the posterior wall of the auricle, short neck, cubitus valgus, limited extension of the elbow, hyperextensible finger joints, redundant skin on the neck and extremities, especially in the hands and feet, deep palmar and plantar creases (Fig. 1b), and hyperhydrosis. Skin folds of the abdominal wall were not prominent. Hair was sparse and short. Results of blood and urinary examinations, including amino acids, organic acids, T3, T4, and TSH, were normal. A lymphocyte karyotype was 46,XY. An EKG showed multifocal supraventricular tachycardia, but echocardiogram was normal. Chest roentgenogram revealed overexpansion. Both cranial CT and skeletal roentgenograms were normal. The infant died of rhabdomyolysis that occurred subsequent to viral infection at age 6 months.

Fig. 1. **a:** Face of patient 1. Note "coarse" face, prominent forehead, hypertelorism, epicanthic folds, depressed nasal bridge, large ears, and short neck. **b:** Hand of patient 1. Note redundant skin and deep palmar creases.

Patient 2

This was a 5-year-old boy. He had typical signs of Costello syndrome, including poor suck, mental retardation, frontal bossing, curly hair, low nasal bridge, redundant skin of the hands and feet, and hyperextensible fingers. Details on this patient have been described elsewhere [Yoshida et al., 1993].

MATERIALS AND METHODS

Pathological Examination

Samples from skin, lung, heart, muscle, and other tissues of patient 1 were obtained by autopsy. The skin of patient 2 was obtained during an operation for Achilles tendon elongation, with the informed consent of his parents. Samples were fixed in formalin, embedded in paraffin, and cut into 6-μm sections.

Northern Blot Analysis

Total RNA was isolated from cultured fibroblasts of patient 1 and from a control individual by the guanidine thiocyanate method. The total RNA (15 μg) was subjected to formaldehyde agarose gel (1%) electrophoresis and then transferred to a nitrocellulose filter. Elastin mRNA was detected by a ^{32}P-labeled elastin cDNA probe, labeled by a multiprimer labeling kit (Takara, Kyoto, Japan). The elastin cDNA probe was kindly donated by Dr. Joel Rosenbloom at school of Dental Medicine, University of Pennsylvania, Philadelphia, PA.

RESULTS

Pathological Findings

Patient 1. Elastic fibers in the skin were fine, disrupted, and loosely constructed. Hyperplasia of the collagen fibers was so prominent that the connective tissue of the corium overgrew under the sweat glands (Fig. 2a,b). Elastic fibers were also fine and disrupted in the tongue, pharynx, larynx, and upper esophagus, but they were relatively preserved in the bronchi, alveoli, aorta, and coronary arteries, although somewhat fine in appearance (Fig. 3a,d). Hyperplasia of mucous glands in the bronchi was observed, and bronchi were filled with mucus. The pulmonary arteries were narrow with diameters about one third those of the corresponding bronchi, but the elastic fibers of the arterial wall were intact (Fig. 3b). There was no emphysematous change in the lung (Fig. 3b). The aorta (Fig. 3d) and coronary arteries were normal except for hyperplasia of the tunica intima in the right coronary artery. In the heart, hypertrophy of the right ventricle and dilatation of the right atrium were observed, but the cardiac muscle exhibited no fibrosis. The conduction system, especially the atrial conduction system and the atrioventricular node, were markedly branched so that the atrium and ventricle were connected with fine muscle fibers proximal to the His bundle and atrioventricular node (Fig. 3c). In skeletal muscle, calcification and ballooning of muscle fibers with infiltration of macrophages were observed. No such changes occurred in the cardiac muscle. The collecting ducts of the kidney

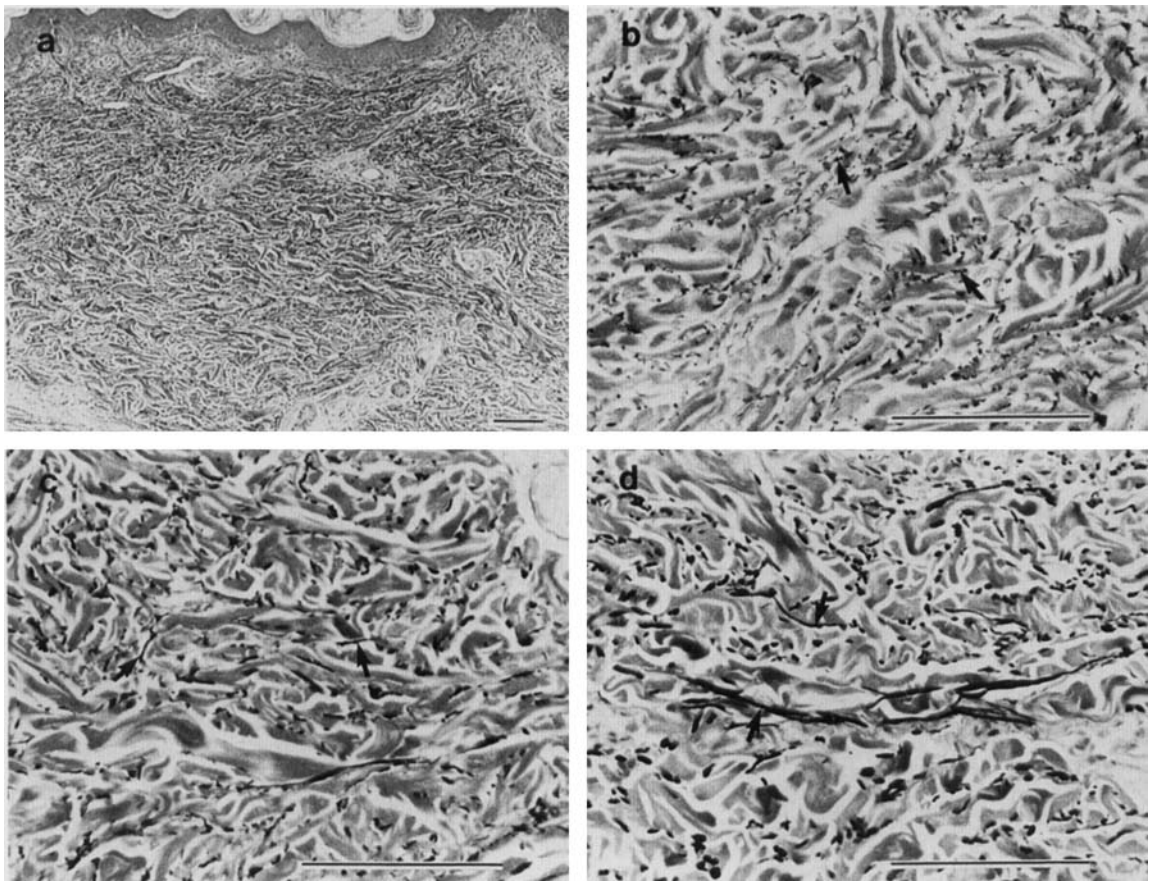

Fig. 2. Skin sections from patients and control. Note thin, loosely constructed and disrupted elastic fibers, and hyperplasia of collagen fibers in the skin of patients, as compared with control. **a:** Low magnification (×100), and (**b**) high magnification (×400) of skin from patient 1. **c:** High magnification (×400) of skin from patient 2. **d:** High magnification (×400) of control skin. Elastica van Gieson staining. Bar, 100 μm. Arrows in (a) and (b) indicate disrupted elastic fibers, and an arrow in (d) indicates elastic fibers in the skin of normal control.

were filled with myoglobin. There was no diverticulum in the intestine and urinary tract. The number of lymphocytes in the thymus was decreased, and microcalcification was observed in the Hassall's corpuscles. There was encephalomalacia of the brain.

Patient 2. Degeneration of elastic fibers and hyperplasia of collagen fibers in the corium were also observed in biopsied skin (Fig. 1c).

Expression of Elastin mRNA in Fibroblasts

Elastin mRNA detected in the fibroblasts of patient 1 had a size similar to that of the control individual. The amount of mRNA was slightly less than that in control fibroblasts, but this difference is probably not significant (data not shown).

DISCUSSION

Since the first description, several cases have been reported, and Costello syndrome has been established as a clinical entity. Unique clinical findings in the skin point to potential involvement of connective tissue in the pathogenesis. The abnormal configurations of elastic fibers in various tissues of our patients are the first described in Costello syndrome, although there are two reports that elastic fibers were intact in biopsied skin from other patients with this syndrome [Patton and Baraitser, 1993; Davies and Hughes, 1994]. The fact that tissues showing disrupted elastic fibers exhibit clinical features such as loose skin and stridor of the pharynx and larynx, and those showing histologically normal elastic fibers (e.g., aorta and pulmonary alveoli) are free from abnormal clinical findings, is consistent with a hypothesis that the abnormal elastic fibers cause these clinical manifestations.

The destruction of elastic fibers has also been reported in cutis laxa and is the fundamental pathologic change [Pope, 1993]. The clinical symptoms of Costello syndrome bear strong resemblance to those of cutis laxa, such as loose skin, dysmorphic facies, herniae, growth retardation, and psychomotor delay [Pope, 1993; Davis and Hughes, 1994]. However, differing distributions of loose skin and patterns of destruction of elastic fibers suggest that these are distinct disorders. The degeneration of elastic fibers of cutis laxa is described as disruption and fragmentation, whereas the elastic fibers of our Costello syndrome patients looked thin, loosely constructed, and disrupted. The involve-

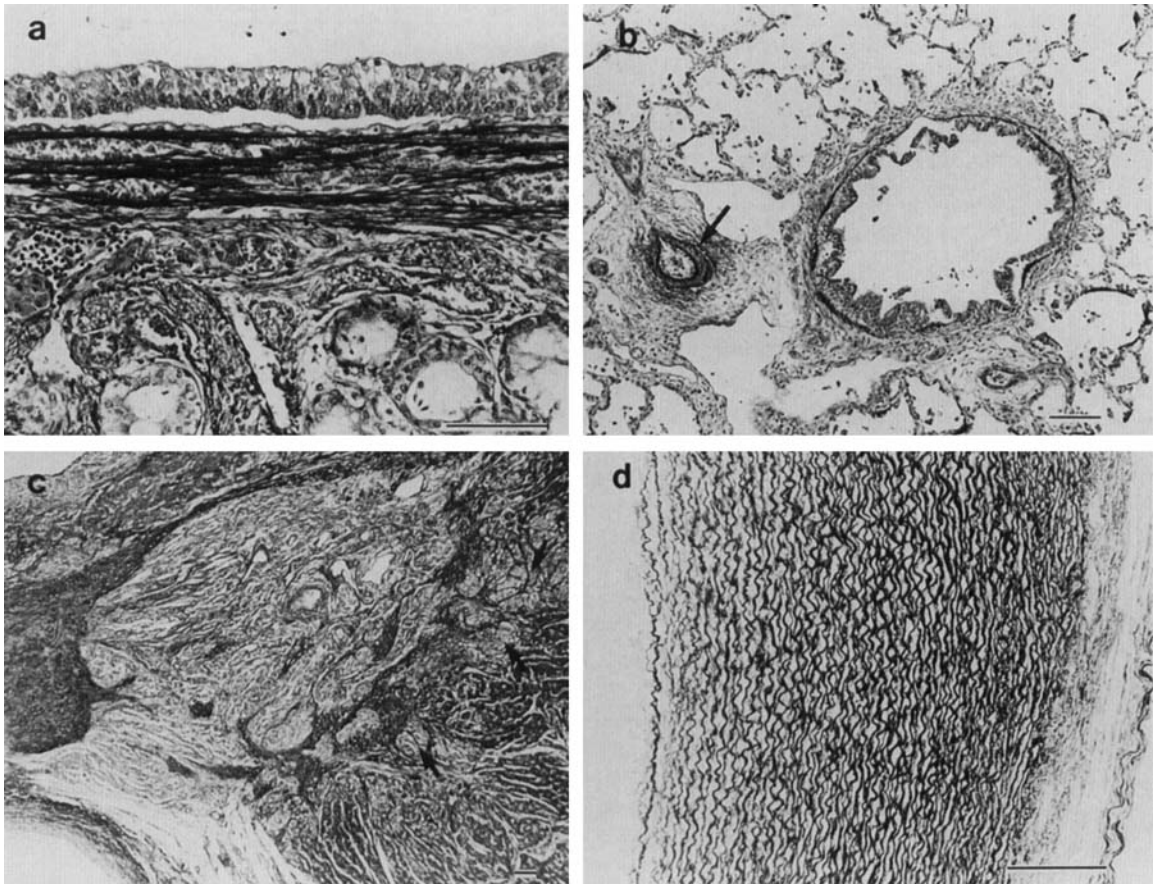

Fig. 3. Histological stains of patient 1. **a:** Bronchus. Elastic fibers are a little fine, but not so disrupted in the mucosa of the bronchus. Note hyperplasia of the mucous glands; the bronchus is filled with mucus. ×200. Elastica van Gieson staining. **b:** Lung. Pulmonary arteries are narrow (arrow), but no emphysematous change is observed. ×100. Elastica van Gieson staining. **c:** Atrioventricular node. Many branched atrial conduction systems (arrows) are observed as collateral routes around the atrioventricular node. ×40. Azan staining. **d:** Aorta. Elastic fibers are normal. ×100. Elastica van Gieson staining. Bar, 100 μm.

ment of elastic fibers in cutis laxa is widely distributed, affecting organs such as the skin, alveoli, aorta, and intestine, while affected elastic fibers were limited to the skin, tongue, pharynx, and larynx in Costello syndrome patients.

Elastic fibers are composed of macromolecules of tropoelastin and associated microfibrils. The human elastin gene is composed of 34 exons, and the major transcribed products are three distinct mRNAs of 3.5 Kb. They are produced by alternative exon splicing, and the distribution and function of these spliced elastins are yet not understood [Indik et al., 1987]. Elastin mRNA was reported to be decreased in fibroblasts from patients with cutis laxa [Olsen et al., 1988; Sephel et al., 1989; Hatamochi et al., 1991], while it was not decreased in Costello syndrome, as shown by our studies. The presence of elastin mRNA of apparently normal size in fibroblasts and the tissue specificity of abnormal elastin fibers in Costello syndrome, indicate that the affected molecular process in Costello syndrome may involve either alternative splicing of the elastin gene or a defect in microfibril assembly.

If a defect of elastin or microfibrils underlies Costello syndrome, could other signs of this syndrome be explained by such a defect? Patient 1 showed dysrhythmia, and his atrial conduction system and atrioventricular node were degenerated. In the heart, degeneration of elastic fibers is known to cause mitral valve prolapse, endocardial elastosis, and rupture of the chordae tendinae. These findings were not observed in this patient, although this might be due to his young age. Cardiomyopathy and systolic murmurs are often observed in Costello syndrome [Costello, 1977; Der-Kaloustian et al., 1991; Berberich et al., 1991; Martin and Jones, 1991; Philip and Mancini, 1993; Teebi and Shaabani, 1993; Borochowitz et al., 1992; Izumikawa et al., 1993; Say et al., 1993; Zampino et al., 1993; Di-Rocco et al., 1993; Johnson et al., 1993]. A role for elastin in the de-

TABLE I. Clinical Findings in Costello Syndrome and in Our Patients

Findings	Reported cases[a]	Patient 1	Patient 2
Polyhydramnios	9/14	+	−
Large for gestational age	8/11	+	−
Poor feeding	13/13	+	+
Postnatal growth retardation	14/14	+	+
Central Nervous System			
Psychomotor delay	14/14	+	+
Cerebral atrophy	4/8	+	
Sociable, warm personality	10/11		−
Facial			
Macrocephaly	11/11	+	+
Coarse face	14/14	+	+
Downslanting palpebral fissures	8/11	+	+
Epicanthic folds	9/9	+	+
Strabismus	5/8	−	−
Depressed nasal bridge	9/10	+	+
Thick lips	13/14	+	+
Macroglossia	5/7	+	
Large mouth	14/14	+	+
Low-set ears with thick lobes	11/11	+	+
Muscloskeletal			
Short neck	11/11	+	+
Increased anteroposterior diameter of chest	10/11	+	+
Herniae	4/5	−	
Elbow limitation	12/13	+	−
Hyperextensible fingers	12/12	+	+
Wide distal phalanges	10/10	+	
Ulner deviation of hands	3/7	−	
Foot positional defects	10/10	−	
Tight Achilles tendon	7/8	−	+
Skin and adnexa			
Curly hair	10/10		+
Thin dystrophic nails	8/9	−	+
Loose skin in hands and feet	14/14	+	+
Deep plantar, palmar creases	12/12	+	+
Hyperkeratotic palms, soles	6/8	+	
Dark skin pigmentation	14/14	−	+
Neoplasias			
Papillomata	7/11	−	−
Other neoplasias	2/4	−	−
Heart			
Hypertrophic cardiomyopathy	6/7	±	
Dysrhythmia	5/7	+	
Heart defects		−	

[a]Costello [1977], Der-Kaloustian et al. [1991], Martin and Jones [1991], Berberich et al. [1991], Philip and Mancini [1993], Teebi and Shaabani [1993], Borochowitz et al. [1992], Di-Rocco et al. [1993], Izumikawa et al. [1993], Kondou et al. [1993], Okamoto et al. [1994], Patton and Baraitser [1993], Say et al. [1993], Yoshida et al. [1993], Zampino et al. [1993]

velopment of the cardiac conduction system should be investigated.

Elastin may have a function in the central nervous system, because patients with Williams syndrome, who have deletions of the elastin gene, show mental retardation. Recently, elastin peptides have been found to facilitate signal transduction via membrane elastin receptors, and this affects the function of macrophages, fibroblasts, smooth muscle fibers, cancer cells, etc. [Senior et al., 1984; Blood et al., 1988; Long et al., 1988]. Perhaps mental retardation in Costello and Williams syndromes arises from a defect in elastin-mediated signal transduction in the central nervous system. The rhabdomyolysis in patient 1 may be related to an altered immune response or muscle membrane composition caused by a defect in elastin.

To determine the relationship between Costello syndrome and elastin abnormalities, further definition of the physiological role of elastin and investigation of elastin in patients with Costello syndrome should be undertaken.

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